

Phytochemical, pharmacological, and biochemical characteristics of essential oil of some *Salvia* L. species

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ABSTRACT

As sciences are advancing, medicinal plants are being increasingly studied for their chemical compounds and the properties of these compounds. Different compounds, with various properties, have been found in plants. The use of the medicinal plants and nature-based compounds in pharmaceutical, cosmetic, health, and food industries worldwide and public attention to the use of medicinal and fragrant plants highlight the need for basic and applied large studies in this area. *Salvia* L. is a large genus in family Lamiaceae. Different species of this genus have highly various essential compounds and amounts of these compounds. Since plant-based secondary metabolites are widely various, this article reported the significance of *Salvia* L. genus and some of its species regarding their essential compounds and pharmacologic characteristics. Presenting the latest important findings, this article summarized the scientific findings about the secondary compounds and pharmacologic and biochemical effects of some species of *Salvia* L.

KEY WORDS: Pharmacologic characteristics, essential biochemistry, *Salvia* L.

1. INTRODUCTION

Nowadays, phytotherapy, the use of plant-based products and plant extracts, is common worldwide. In different countries, the growing increase in the use of drugs and the side effects caused by synthetic drugs that contribute to environmental pollution have led to a considerable increase in the public acceptance of phytotherapy (Omidbaigi, 2006; Rafieian-Kopaei, 2012). Labiatae or Lamiaceae is a big family of plants with global distribution (except northern and southern regions). This family consists of 200 genera and over 4000 species that occur almost everywhere in the world, especially Mediterranean region, and have very different ecological needs and life forms. Family Lamiaceae has several herbaceous, decorative, and edible plants that are used to produce essences (Zarezadeh, 2007). In this family, there are different genera, some of which are important pharmaceutical and spice species including *Betonica*, *Clinopodium*, *Dracocephalum*, *Nepeta*, *Stachys*, *Teucrium*, *Zhumeria*, *Salvia*, *Satureja*, *Thymus*, *Zataria*, *Ocimum*, *Origanum*, and *Hyssopus*. Several medicinal species of family Lamiaceae are used to treat diseases. Some of these species contain essence and many of them are edible (as raw or cooked) or are cultivated because they have beautiful and fragrant flowers (Mozaffarian, 2011). The medicinal and aromatic plants of family Lamiaceae are considered an important herbal genetic reserve because of having a high ecological flexibility to various climates. These plants are frequently used in cosmetic industry because of containing widely various fragrant compounds (Zargari, 1990). As the medicinal plants are increasingly being investigated worldwide and several plant-based drugs are commercially available, it is necessary more than ever to study the medicinal plants and their effective substances. Since many useful medicinal plants occur in Iran, investigating the effective compounds of these medicinal plants and their therapeutic effects can be a positive step to identifying and efficiently using this national asset. Recently, the plants and some genera of the family Lamiaceae, including *Salvia* L., have been investigated for their essential compounds. Given the climatic diversity and environmental variations in different regions of the country that affect the type and amount of the essential compounds of the plants, this study considered and compared the phytochemical and biochemical essential compounds of four important and commonly used species of *Salvia* L. Offering the latest important findings, this study concluded the results of scientific investigations on the secondary compounds and pharmacologic and biochemical effects of these four species.

Genus *Salvia* L: *Salvia* L. is considered a large genus of family Lamiaceae with 700 species occurring worldwide and 58 species occurring in Iran. The species of this genus have highly various amounts and types of essential compounds. Therefore, they are variously used in pharmaceutical, cosmetic, and food industries depending on the type and percentage of the essential compounds (Batooli, 2013). The word *Salvia* is derived from the Greek word *Salver* meaning healer or healing and representing the multiple medicinal uses of this family (Ebrahimabadi, 2010). Most species of *Salvia* L. are woody and herbaceous shrubs with very fragrant aerial organs. The leaves of *Salvia* L. plants are widely known as medicinal plants. Worldwide, *Salvia officinalis* L. (Figure 1) is the most famous species of *Salvia* L. The leaves of *S. officinalis* are used as potent energizing medicinal plants and strengthening, anticonvulsant, disinfectant, and glycemia-regulating agents. The essence of *S. officinalis* flowering shoots is used in scented soaps in perfumery (Batooli, 2013; Kermavshah, 2009). The pharmaceutical properties of *Salvia* L. species are widely known and used to treat common cold, skin injuries and infections, headache, anemia, memory disorders,

bronchitis, gastrointestinal diseases, tuberculosis, and hepatitis (Rauter, 2012). Several studies of different species of *Salvia* genus have demonstrated the antibacterial, antifungal, antitumor, antioxidant, and anti-inflammatory of these plants (Kelen, 2008; Hosseinzadeh, 2003). In addition, different species of this genus have been reported to contain flavonoids, diterpenoids, and sesquiterpenes. To date, decomposition of the essences of many of the species of this genus has been conducted in several investigations (Bigdeli, 2005; Abravesh, 2005; Esmaeili, 2007; Habibi, 2004).



Figure.1. *Salvia officinalis* L.

Botanical characteristics of some *Salvia* L. species: *Salvia officinalis* L. is a perennial and herbaceous plant reportedly originating from northern Mediterranean regions and northern Africa. This plant is from Lamiaceae family, with root, many branches and a 50- to 80-cm height. Tujan (35-60%), cineole, borneol, and borneol acetate are the main compounds of *S. officinalis*. In food industries, *S. officinalis* is used as spice and flavor and the flowers of this plant are used as a type of beverage such as tea. In pharmaceutical industry, *S. officinalis* is frequently used as antispasmodic, anti-astringent, disinfectant, antibiotic, sedative, liver-stimulating, and digestive. Recently, the *S. officinalis* essence, especially some compounds of this plant such as 1, 8 cineole, tujan, and kaempfer, has been reported to exert antimicrobial, antioxidant, and anticancer effects (Mozaffarian, 2011; Eidi, 2005). Regarding geographical distribution in Iran, *S. officinalis* occurs in Azarbaijan, Lorestan, Shiraz, Kermanshah, Semnan, and Damavand of Tehran province. Certain species such as *Salvia hypoleuca*, *Salvia sahendica*, *Salvia urmiensis*, and *Salvia persepelinata* are native to Iran. Other species may also occur in Middle East, Afghanistan, Turkey, and Egypt. (Karami, 2015). This plant may be cultivated in gardens because of having beautiful appearance and flowers with attractive colours (Aktas, 2009). *Salvia macrosiphon* is a herbaceous and perennial plant with a square stem. The corolla is white, erratic and continuous with lengths of 2-2.5 cm, flowers are bisexual and single based, corolla tube is 5.8 mm long. Five continuous, bluebell-shaped sepals, the leaves' margins are congress- or crescent-shaped, the leaf tip is narrow and leaf base is asymmetric heart-shaped (Bakhshi Khaniki, 2008). *Salvia limbata* is a perennial, fragrant, square plant, with a height of about 60-30 cm and bushy appearance, bright green, crossed, thick leaves with networks of veins. The veins on the lower surface of the leaf are apparent. The flowers of this plant may be light blue, purple, pink, white, or yellow and usually appear in the summer of the second year. For the amount of essence in the flowers, the best time of harvesting is the beginning of the flowers' emerging. The essence which is obtained from the wild species of this plant is a yellow or greenish yellow liquid and has a specific smell. The time of *S. limbata* flowering is Ordibehesht and Khordad (Mozaffarian, 2011). *Salvia macrochlamys* is a perennial and herbaceous plant with 30- to 50-cm height, simple and ovular leaves, 2- to 4-cm petioles, reddish white, 35-cm petals, and abundant flowers and braquets in stem with two flowers vertical to stem. In Iran, this plant is distributed in Azarbaijan (Rechinger, 1982).

The essence or aromatic compounds: Essence or aromatic compounds are a large and important group of secondary biochemical compounds in the medicinal plants and spices, especially aromatic plants. The findings have indicated that approximately 2000 plant species from 87 families are able to produce essence, including Lamiaceae, Apiaceae or Umbellifera, Asteraceae or Composite, Rutaceae, Myrtaceae, Lauraceae, Rosaceae, Magnoliaceae, and Pinaceae (Ghasemi-pirbalouti, 2008). The amount of the essences obtained from the plant species varies between 1 and 20% of the fresh plant's weight depending on genetic, environmental, and technical characteristics and the methods of essence extraction. Although the amount of the obtained essences from some plants is very small, they enjoy a high economic value because of their significance and wide use in traditional and modern pharmacology, perfumery, cosmetic industry, food industries such as plant-based antioxidants, reduction of spoilage of foods, beverage, spices and flavors of foods, and control of pests and plant diseases (Ghasemi-pirbalouti, 2008; Omidbaigi, 2006).

Phytochemical characteristics of the essences of *Salvia* L. species: Overall, most volatile oils are composed of isoprenoid compounds which are composed of isoprene subunits (except allyl isothiocyanate, organic phosphorous compounds, mercaptans, indole derivatives, and some phenolic compounds). Monoterpenes, sesquiterpenes, and diterpenes are the result of combining 2, 3, and 4 isoprene subunits $\text{CH}_2=\text{CH}-\text{C}=\text{CH}_2$, respectively (Fatahie, 2009). Terpenes are composed of the cyclical subunits. The terpenes composed of two and three isoprene subunits and

monoterpenes are referred to as sesquiterpenes. The molecules of terpenes may be linear or annular. Many of the terpenes which have been identified in the plants have a specific smell or taste. The essences are known as terpenes or terpene-based. Usually, they have a pungent smell and taste and a low-than-water special weight. Essences may be found in individual or accumulated excretory cells, excretory glands and ducts, and on the surface or within different organs (Omidbaigi, 2003). To date, different studies have been conducted on the decomposition of the essences of *Salvia L.* species. In one of these studies, the essence of aerial organs of *Salvia lereifolia* gathered from Sabzevar, Iran was investigated by GC and GC/MS and 22 compounds were identified. The most significant compounds of this essence were 1, 8-cineol (16.2%), beta-pinene (23.1%), alpha-pinene (13.8%), and alpha-candinal (9%) (Rustaiyan, 2000). In the studies of *S. officinalis*, linalool (22-32%) and linalool acetate (25-51%) were found as the most significant compounds (Dzumayer, 1995). In addition, 43 essential compounds were identified in the aerial organs of *S. officinalis*, most important of which were beta-pinene (16%), borneol (9.4%), alpha-humulene (8.4%), and globulol (9.3%) (Rustaiyan, 1997). Studies have shown that the majority of the plants of family Lamiaceae are highly rich in phenolic compounds and the antioxidant and polyphenolic properties of these plants were demonstrated. Rosmarinic acid, carnosic acid, salvianolic acid, rosmanol, epirosmanol, rosmadial, and methylcarnosate are the phenolic compounds reported to be present in different *Salvia L.* species (Batooli, 2013). Given the findings of the studies investigating the main compounds of different *Salvia L.* species, germacrone-D, spetanol, germacrone-B, beta-caryophyllene, caryophyllene oxide, B-cyclogermacrone, and isospetanol are the most significant sesquiterpenes reported to exist in these species' essences (Rustaiyan, 2007; Yousefzadi, 2007; Ogutcu, 2008). Flandern, sabinene, alpha- and beta-pinene, trans-beta-ocimen, limonene, linalool acetate, linalool, alpha-terpineol, and geranyl acetate were reported to be the most important monoterpenes of the essences of *Salvia L.* species (Feorkas, 2005; Gulcin, 2004). Diterpenoids, triterpenoids, and flavonoids are the main constituents of the secondary metabolites of *Salvia L.* species (Min-Hui, 2008; Başkan, 2007). Phenolic acids and their derivatives are present in all species and are involved in several bioactivities. Caffeic acid plays a pivotal role in the biochemistry of family Lamiaceae and is the constructive subunit of various phenolic metabolites, ranging from simple monomers to various oligomeric products (Wang, 2013). Rosmarinic acid is the most abundant dimer of caffeic acid and the most important phenolic compound to which the antioxidant activity of *Salvia L.* species is attributed. The trimer and tetramer forms of caffeic acid are highly important from pharmaceutical perspective because of enjoying unique biological characteristics. Caffeic acid-derived trimers are the largest group of secondary metabolites in *Salvia L.* *Salvianolic acid A* is one of these trimers with antioxidant, antitumor, and biological membrane-protective properties *Salvianolic acid B*, a dimer of rosmarinic acid (Figure 2) and a tetramer of caffeic acid (Figure 3), is frequently found as ammonium, potassium, and magnesium salts. These derivatives of caffeic acid are the most abundant hydrophilic compounds of *Salvia L.* species.

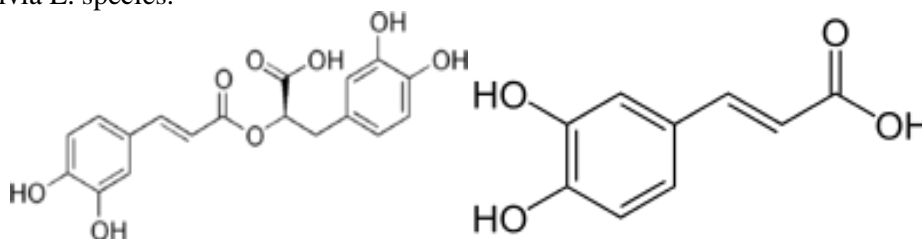


Figure.2. Rosmarinic acid structure Figure.3. Caffeic acid structure

Fatty acids and esters are other important pharmaceutical metabolites of *Salvia L.* species. Fatty acids play a fundamental role in the body's metabolism and are involved in forming important compounds such as prostaglandins, leukotrienes, and thromboxanes (Haghir Ebrahimabadi, 2007). Some studies have shown that palmitic acid (C16:0, PA), stearic acid (C18:0, SA), OA, LA, and ALA are the prominent fatty acids of the oil of *Salvia L.* plants' seeds (Azcan, 2004; Bagci, 2004; Ayerza, 2004; Kurşat, 2013). Furthermore, triterpene, alkaloids, tannins, and quinines have been reported to exist in *Salvia* species and glycosides, cyanogenic, and saponins were not found in these species (Ulubelen, 1996). Table 1 gives some details about the locations of gathering, the used organs, and the methods of essence extraction of these four species. The most significant essential compounds of *S. macrosiphon* flower have been limonene (6.9%), alpha-pinene (6.8%), spathulenol (6.8%), myrcene (6.7%), beta-caryophyllene (5.6%), and beta-pinene (4.9%). The main essential compound of *S. macrosiphon* flower and leaf is limonene (6.9%) and myrcene (8.1%), respectively. The main essential compound of *S. limbata* flower and leaf is spathulenol (7.4%) and myrcene (7.2%), respectively (Bakhshi Khaniki, 2008). There have been scant reports on phytochemical characteristics of *S. limbata*. The chemical essential compounds of this plant have been investigated by GC/MS and GS. Spathulenol, limonene, alpha-pinene, beta-caryophyllene, myrcene, and beta-pinene are the most significant essential compounds of *S. limbata*. The monoterpenes of *S. limbata* are salvininorin A-F, ursolic acid, carnosic acid, carnosole, and tanshinone and the flavonoids of this plant are hispidulin and epigenin (Gohari, 2010). To date, over 42 chemical compounds have been identified in this plant's extract, including sclareol oxide (14.8%),

spathulenol (29.3%), 1,8-cineol (3.2%), and beta-eudesmol (7.4%). To date apigenin, luteolin, caffeic acid, ursolic acid, diterpene, cosmosiin cynaroside, and dinorsesterterpenes have been isolated from *S. limbata* in phytochemical investigations.

Table.1.The data of the studied species

| Species | Places of gathering | Time of gathering | Used organs | Methods of essence extraction | Reference |
|----------------------------|------------------------------|-------------------|------------------|-------------------------------|-------------------------|
| <i>Salvia macrosiphon</i> | Dodangeh village (Boroujerd) | Late Ordibehesht | Leaf and flower | Distillation | (Bakhshi Khaniki, 2008) |
| <i>Salvia limbata</i> | Dodangeh village (Boroujerd) | Late Ordibehesht | Leaf and flower | Distillation | (Bakhshi Khaniki, 2008) |
| <i>Salvia macrochlamys</i> | (West Azarbaijan province) | Khordad | Flowering shoots | Distillation | (Kazemizadeh, 2008) |
| <i>Salvia officinalis</i> | National Botanical Garden | Late spring | Flower | Steam distillation | (Rasooli, 2000) |

Pharmacological and therapeutic properties of *Salvia L. species*: *Salvia L.* has several clinical properties and has long been used as a medicinal plant (Farhoudi, 2011). Initially, it was used as an effective drug to treat the complications due to insects' bite as antidote, as a tonic and strengthening drug for soul and body, and to increase longevity. Currently, the essence of *Salvia L.* is used to flavor canned meat, sausages, and chicken and to be mixed, as base oil, with other essential oils in perfumery (Jibao, 2006; Pavela, 2005). This plant is used to treat common cold, cancer and as hypoglycemic (Behradmanesh, 2013; Eidi, 2005). To strengthen muscles and to calm the nerves. Other therapeutic properties of *Salvia L.* are gastrointestinal tract-stimulating to digest food and bile-secreting. Moreover, *Salvia L.* essence has been recently reported to exert antibacterial property because of 1- and 8-cineole (Yousefzadi, 2007; Salehi, 2007). The study of the antimicrobial activity of *Salvia limbata* and *Salvia sclarea* occurring in Turkey indicated that the essence of *S. limbata* had a greater antibacterial effect than *S. sclarea* (Ogutcu, 2008). Moreover, the essence of leaf, stem, and flower of *Salvia L.* occurring in Isfahan, Iran had favourable effects on seven bacterial strains (Esmaeili, 2008). Some studies on children with congenital heart disease have indicated that intravenous injection of *Salvia L.* extract caused decrease in the serum level of creatinine kinase (Xia, 2003). The findings of some studies demonstrated that the extract of *Salvia L.* root prevented development of liver fibrosis in mice (Nan, 2001). Furthermore, the extract of *Salvia L.* affects the regulation of expression of alkaline phosphatase (Liu, 2007; Chien, 2011). Besides that, the investigations have indicated that the extract of this plant is effective on the function of liver enzymes of mice (Zhanq, 2009). The *Salvia L.* is able to affect the behavioral skills of humans. Therefore, it can be used to treat Alzheimer's disease (Akhondzadeh, 2003). The use of this plant helps to decrease glycemia and can be effective in treating hepatic, renal, and inflammatory diseases (Zhanq, 2009; Kianbakht, 2011). The extract of *S. officinalis* is effective in improving memory (Savelev, 2004). *S. officinalis*, according to traditional medicine, has cholinergic connection, mood-regulating, and cognitive function-related properties *in vitro* in the human body and therefore is considered a new therapeutic approach to treat Alzheimer's disease (Miyazawa, 2005). The association between the *S. officinalis* extract and the cholinergic system is related to the presence monoterpenes such as sabinene, alpha-terpinene, sesquiterpenes such as gamma-kadinene, alpha-muurolene, beta-muurolene, and three diterpenes, neophytadiene, phytol, velgarol, in this plant (Kolak, 2011). This plant can affect morphine withdrawal syndrome. Diazepam (5 mg/kg) and the methanol extract of *S. limbata* leaf (1000 mg/kg) had a similar effect on the decrease in the frequency of jumping of Balb/C mice with morphine withdrawal syndrome (Karami, 2012, 2013). In a study to investigate the effect of the *Salvia L.* extract on the damage to pancreatic tissue of diazinon-poisoned rats, the extract caused the number and diameter of cells and blood vessels of pancreatic tissue to increase compared to the diazinon-poisoned rats and was demonstrated to exert favourable effects on fighting oxidative activities in the body. As a result, the *Salvia L.* extract may help to strengthen the antioxidant system of the body through eliminating free radicals and diazinon-induced oxidative stress (Fattahi, 2015). The extract of *Salvia L.* is able to inhibit the growth of colorectal cancer cells in cell culture (Slamenová, 2004). The diterpenoid quinines extracted from *Salvia L.* have cytotoxic effects and can damage the DNA of colon and liver cancer cells in cell culture and therefore inhibit the growth of tumor cells (Keshavarz, 2011). In addition, the study of the *Salvia L.* species' effect on corio-allantois membrane of chickens demonstrated the anti-angiogenic and anti-proliferative activity of this plant's extract. Alpha-terpineole which is a main compound of *Salvia L.*, can help to inhibit the growth of tumor cells and hence the secretion and release of the CEA marker tumor (Sertel, 2011). Furthermore, some compounds of *Salvia L.* extract, including tugen monoterpenes, beta-pinene, and cineole, can play a role in treating cancer by inhibiting the cell growth (Janicsak, 2011). Moreover, the essential oils of the *Salvia L.* extract have antitumor activity (Hassan, 2010).

2. CONCLUSION

Given the side effects of chemical drugs, potentially developed after use, and the cost of mass production of synthetic drugs, the secondary compounds of the medicinal plants can be suitable alternatives to the synthetic drugs. Human beings have constantly seeking out the substances and drugs to treat diseases and relieve diseases' symptoms. Relevantly, the medicinal plants have long and traditionally been used by different ethnics and nations. Since many useful medicinal plants occur in Iran, the study of the effective compounds and pharmaceutical effects of these plants can be an important step to identifying and efficiently using this national valuable asset. This study indicated that the plants of *Salvia L.* genus had a high potential and can be effective treatments for many diseases. Furthermore, many of the properties of *Salvia L.* genus plants, including antibacterial, antitumor, antioxidant, and anti-inflammatory, are due to the presence of diterpene chemical compounds in different species of *Salvia L.* Rosmarinic acid is the most abundantly found caffeic acid dimer and the most significant phenolic compound in *Salvia L.* *Salvia L.* seed contains large amounts of plant-based esters, especially beta-sitosterol. Therefore, the seeds of this plant may have pharmaceutical and food uses. The findings have indicated that the most significant monoterpenes found in the essences of different species of *Salvia L.* are flandern, sabinene, alpha- and beta-pinene, trans-beta-ocimene, limonene, linalool acetate, linalool, alpha-terpineole, and geranyl acetate. In addition, terpenoids and flavonoids are the main constituents of the secondary metabolites of *Salvia L.* species. Some of the essential compounds are common to different species of *Salvia L.* and the difference in the amount of the chemical essential compounds among different species of *Salvia L.* may be attributed to the methods of the essence extraction, the location and time of gathering the plants, the used organs, the methods of drying the plants, and other environmental and genetic factors.

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